REMARKS

Claim 1 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner states that the term "dense core element" coated with a solid reservoir medium containing DNA pharmaceutical agent is confusing.

The Examiner is correct in saying that the specification states that the "dense core element" is **preferably** (emphasis added) a small metal bead suitable for ballistic delivery of the agent into a cell. Thus "dense core element" is not limited to a small metal bead, but a small metal bead is only preferred. The specification read as a whole makes it clear that the term 'element' is not intended to be limited to the chemical definition of the word i.e. an element of the periodic table, or indeed "'a heavy element such as gold or tungsten" as the examiner interprets. The specification as a whole teaches that the core must be dense enough to allow penetration of the epidermis. There is no requirement for it to be a chemical element. Page 10, final paragraph of the application as filed states that "The core elements impart upon the final dosage form sufficient strength and momentum to pierce the stratum corneum in any given ballistic device." Such is the only requirement for dense core element.

Claims 1-20 have been rejected under 35 U.S.C. 103(a) as unpatentable over Tuting & Albers in view of Roser et al (US Patent 6,290,991 B1), and Vokin et al (WO 97/40839 A1). The Examiner states, inter alia,

> *One of ordinary skill in the art would have had a reasonable expectation of success when modifying the DNA pharmaceutical dosage form (i.e. DNA coated gold particles or microcarriers) of Tuting & Albers by the combined teachings of Roser et al. and Volkin et al., because they provide explicit disclosures about (1) the use of stabilizing, amorphous, biodegradable, polyol glass made of sugars such as trehalose, loaded with the bioactive materials and capable of releasing the bioactive material in situ; and (2) the use of stabilizing agent such as a metal ion chelator (EDTA, TRIS, as recited in claim 4) and/or a non-reducing free radical scavenger (ethanol or methionine) that inhibit the degradative effects of free radicals, in order to preserve the supercoiled structure of the plasmid DNA and also to increase the ability to store the pharmaceutical DNA agent for longer period of time at 37°C. Given the benefits accrued by adapting the modifications taught by both, Roser et al. and Volkin et al. for improving and stabilizing the DNA pharmaceutical agent dosage form of Tuting & Albers, one of ordinary skill in art would be motivated to make such modifications in the delivery vehicle or formulations to optimize the efficiency of DNA vaccine delivery using various administration techniques (such as ballistic delivery to skin tissue) that use solid DNA pharmaceutical agent dosage forms such as claimed in the instant invention.*

Tuting & Albers discloses a basic gene gun. The DNA is delivered by means of a small gold bead which is coated with plasmid DNA encoding genes of interest. This differs from the delivery vehicle of the invention in the means by which the DNA is attached to the gold bead - the attachment means of the present invention is by coating such a bead with a solid resevoir medium, e.g. sugar glass containing the DNA, and it also differs in that the DNA of the invention is stabilized by the addition of free radical scavengers/ion chelators.

Roser et al has no disclosure of a bead coated with DNA, and does not address any issues of stability of DNA. It is directed to delivery of bioactive particles using sugar glass (trehalose etc) with the bioactive substance embedded within the sugar glass. Several routes of delivery are given for such particles, including transdermal delivery via a ballistic device (PMED). However, there is no suggestion that this sugar glass could be used to coat a dense core element. It is merely an alternative to a bead coated with DNA. There is no incentive to combine this with the disclosure of Tuting & Albers, furthermore there is no incentive to modify the disclosure of the sugar glass to use it for coating a bead.

The third document - Volkin et al discloses nucleic acid vaccines. It does not discuss PMED technology, but instead is directed to the use of free radical scavengers and ion chelators in stabilising DNA for use in vaccination. There is no indication that stabilising the DNA in such a way would be suitable for a DNA formulation which is coated on to a bead for use in PMED delivery. Furthermore the skilled man would not think it obvious that a formulation could work which comprises the ion chelators/free radical scavengers combined with the sugar solid resevoir medium from a starting point of plasmid DNA coating a bead because there would be some doubt as to whether the sugar glass could be created with the other stabilising excipients present, as this might change the properties of the glass. The skilled man may also question whether the ion chelator and free radical scavenger would work when locked into a glass structure. Thus, there is no reason for the skilled man to combine both these methods of stabilising DNA if the application of one or other of the methods would produce a sufficient stabilising effect as is suggested by each of these documents independently.

The examiner alleges that it would be obvious to combine the teachings of the two documents (Roser and Volkin) and apply them to Tuting and Albers. However, there is no incentive to improve the system by stabilising the DNA or altering the attachment means, so it would not have been obvious to combine the teachings of these three documents, and it certainly wouldn't have been obvious to then adapt the modifications taught by these documents to arrive at the delivery vehicle of the present invention.

In view of the above remarks, reconsideration of this application is requested. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned agent at the number below.

Respectfully submitted,

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